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# US ARMY MEDICAL RESEARCH LABORATORY

FORT KNOX, KENTUCKY 40121

REPORT NO. 769

CO<sub>2</sub> LASER INDUCED SKIN LESIONS

(Final Report)

by

Arnold S. Brownell, Ph.D.

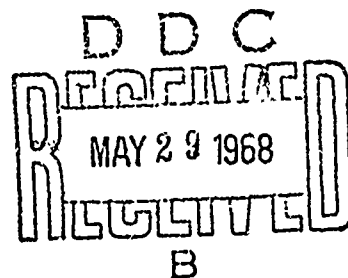
Wordie H. Parr, Ph.D.

Captain David K. Hysell, VC

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13 March 1968



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UNITED STATES ARMY  
MEDICAL RESEARCH AND DEVELOPMENT COMMAND

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US ARMY MEDICAL RESEARCH LABORATORY

Fort Knox, Kentucky 40121

13 March 1968

Cutaneous and Deep Burns Induced by Laser Radiation

Work Unit No. 103

Surgery

Task No. 01

Research in Biomedical Sciences

DA Project No. 3A014501B71R

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USAMRL Report No. 769  
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## ABSTRACT

### CO<sub>2</sub> LASER INDUCED SKIN LESIONS

#### OBJECTIVE

To define skin response to different exposure time-irradiance combinations using CO<sub>2</sub> laser radiation (10.6  $\mu$ ).

#### METHODS

Lesions ranging from a mild erythema to partial tissue coagulation were produced on depilated porcine skin. Exposure times for a given irradiance with a 50 percent probability of producing a particular grade of lesion were then established.

#### RESULTS AND CONCLUSIONS

The dose-response relationships for producing different grades of cutaneous burns were determined for power densities within the range of 0.69 to 13.6 watts/cm<sup>2</sup> and exposure times of 0.2 to 40 sec. The data obtained are adequate to establish safety standards for cutaneous injury within these ranges. A relatively simple model which describes the exposure parameters to produce threshold skin lesions within the reported range is discussed.

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## CO<sub>2</sub> LASER INDUCED SKIN LESIONS

### INTRODUCTION

A recent report by Brownell *et al* (1) presented data defining a set of exposure conditions necessary to produce minimal detectable lesions in porcine skin with radiation from a CO<sub>2</sub> laser. They found that the relationship between irradiance and exposure time was approximately described by a simple power function of the form  $H = at^{-b}$  where  $H$  is the incident irradiance,  $t$  is the exposure time, and  $a$  and  $b$  are empirical constants. However, the relationship was determined only for the limited range of irradiance extending from 1.5 to 8 watts/cm<sup>2</sup>. Additional measurements have indicated that outside this range the dose-response relationship may change and can no longer be described by the same equation.

This study was conducted to extend the range of the dose-response relationship to higher and lower irradiance levels than the previous report. In addition, the exposure parameters were determined for burns more severe than the minimal erythema.

### METHODS

Except where noted, the methods and equipment used in this investigation have been described in detail elsewhere (1). The CO<sub>2</sub> laser was designed and constructed by the Martin Marietta Corporation (2). The laser output was routinely measured with an inverted cone calorimeter which was calibrated against a constant flow water calorimeter with a silver chloride window, both of which were designed and constructed at this laboratory. The beam size was limited by an aperture to 19 mm diameter at the target site, except for the irradiance levels of 10.6 and 13.6 watts/cm<sup>2</sup>. In the case of experiments involving these two irradiance levels, the beam was focused and recollimated by 80 cm and 45 cm focal length lenses which produced beam diameters of 14 and 16 mm, respectively, at the target site.

In order to achieve the power densities required over a reasonably large area it was necessary to adjust the laser for highly multimoded operation. The resulting output beam consisted of an array of closely spaced regions of rather sharply peaked energy flux distribution (see reference 1 for a more detailed discussion of energy distribution within the laser beam). It was estimated that the energy distribution within the output beam ranged within plus or minus 25% of the measured average value.

The power output of the laser was very stable except when it was reduced to the point where the power density was about 1 watt/cm<sup>2</sup> or less at the target site. Under these conditions the output tended to decrease slowly and in two cases decreased as much as 20% during the experiment.

Fifty-nine pigs, with pigment-free skin, were used in the experiments. Their weights averaged 37 pounds. Acepromazine and pentobarbital sodium were given as the preanesthetic and the anesthetic, respectively. The skin area to be exposed was closely clipped and cleaned. The area was then divided into four rows and ten columns, providing a grid of 40 squares. Figure 1 illustrates the placement of the grid pattern and burns. Three to eight animals were used for each irradiance level. To minimize variation in area to area sensitivity, the exposure times within each irradiance group were randomly assigned to the grid pattern. Each irradiance-exposure time combination was generally replicated 10-20 times with each animal within a group receiving approximately the same number of exposure combinations. The room temperature was held within 72-78°F in order to reduce the influence of ambient temperature (3).

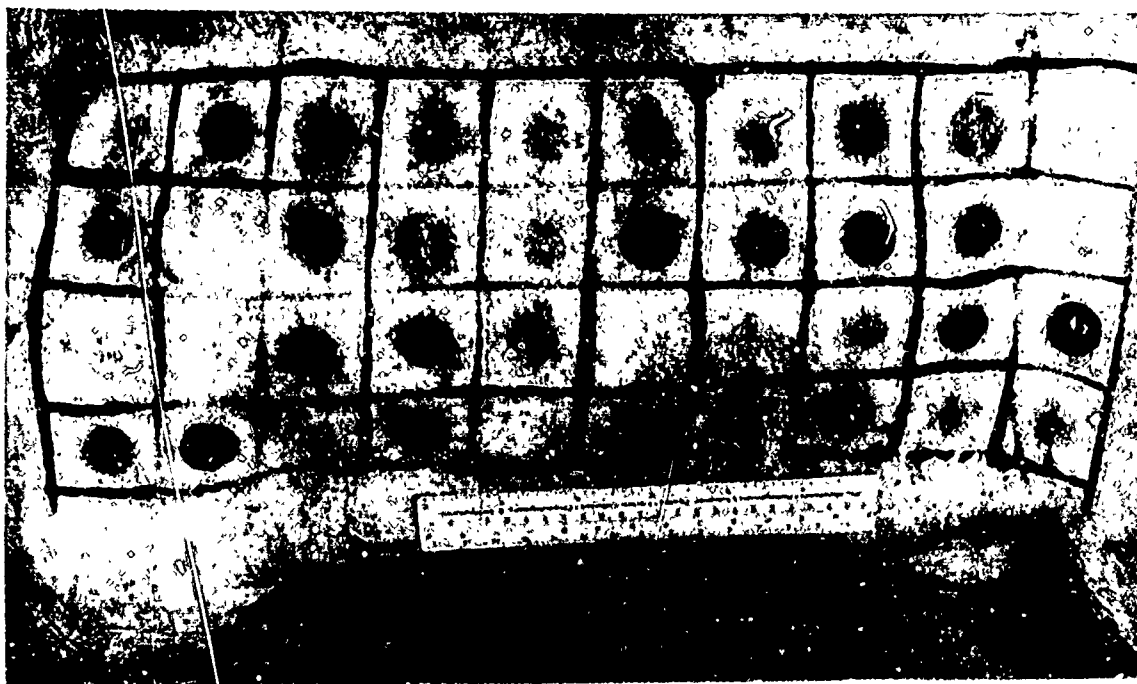


Fig. 1. Porcine skin immediately following exposure to laser radiation of 2.5 watts/cm<sup>2</sup> and exposure times of 1.4 to 5.2 sec.

Subtle differences in color, intensity and uniformity of the surface appearance of the lesions were used to evaluate the severity of the cutaneous burns. The categories used were:

- 0 No detectable change
- 1 Erythema (red burn)
  - 1-1 Erythema, disappears within 18-24 hr
  - 1-2 Mild erythema
  - 1-3 Moderate erythema
  - 1-4 Severe erythema with bluish cast
- 2 Coagulation (white burn)
  - 2-1 Spotty coagulation
  - 2-2 Uniform white burn

The final evaluations of the burns were made 18-24 hr after exposure.

The median effective exposure time ( $EET_{50}$ ) was determined graphically for each subdivision of burn severity at each irradiance level used by the probit method of Litchfield and Wilcoxon (4). The  $EET_{50}$  is the exposure time for a given irradiance with a 50% probability of producing a given grade of lesion.

Biopsies were taken from a selected number of lesions for histological and histochemical evaluation in order to determine the correlation between the microscopic and surface appearance of the lesions (5).

## RESULTS

The data obtained from the gross evaluation of 2,288 porcine skin burns are presented in Table 1 (page 12). The number of burns in each grading classification is listed for each irradiance-exposure time combination used. For this report grades 0 and 1-1 were combined since both represent undetectable lesions 18-24 hours post-exposure.

In almost every instance, either during or immediately following the exposure period, the skin at the exposure site developed a diffuse, transient erythema. This erythema usually extended beyond the limits of the exposure site. In general, the longer the exposure time the longer this transient erythema persisted. In the case of burns which persisted beyond 24 hours the peripheral erythema subsided, leaving a well marked lesion closely corresponding to the size of the laser beam.

From the data in Table 1 the median effective exposure time ( $EEt_{50}$ ) has been determined for each subdivision of burn severity at each irradiance level used. The results are presented in Table 2 (page 17). Since the data for 2-1 burns at irradiances of 1.1 and 1.2 watts/cm<sup>2</sup> were too limited for meaningful calculations of confidence limits, approximate  $EEt_{50}$  values were determined by extrapolating the available data to the 50% probability level. The extrapolation was accomplished by using the slope of curves for other grades of burn in the same series. No 2-1 burns were produced with an irradiance of .69 watts/cm<sup>2</sup> for the exposure times used.

Effective exposure times for other than the 50% level may be determined from the data in Table 2 by use of the slope function  $S$  as defined by Litchfield and Wilcoxon (4). The effective exposure times at the 16% and 84% probability level may be calculated as follows:

$$EEt_{16} = EEt_{50} \div S$$

$$EEt_{84} = EEt_{50} \times S$$

The mean slope function for the data in this report is  $1.16 \pm 0.05$ ; values of  $S$  calculated for different groups of irradiance or burn grades did not differ statistically. A straight line drawn through the 16% and 84% points plotted on logarithmic probability paper provides a curve from which the approximate  $EEt$  can be determined for any probability level desired.

The data in Table 2 are presented graphically in a log-log plot in Figure 2 (next page). A power function such as  $H = at^{-b}$  when graphed as log-log plot yields a straight line; however, it can be seen in Figure 2 that the slope of the curve for threshold lesions changes at high and at low irradiance levels. It is apparent that this simple power function is inadequate to describe the relationship between irradiance and exposure time for even the limited range of exposure conditions tested here.

The curves for the more severe burns show the same general trends as that for mild erythema. Note that the curves for the various grades of burns tend to converge at the longer exposure times. It is quite obvious from the graph that for longer exposure times a relatively small increase in irradiance can make a difference between a mild and a severe burn.

The data in Table 2 for mild erythema (1-2) and partial coagulation (2-1) have been used to calculate the median effective radiant exposure as a function of exposure time for the two levels of burns. The



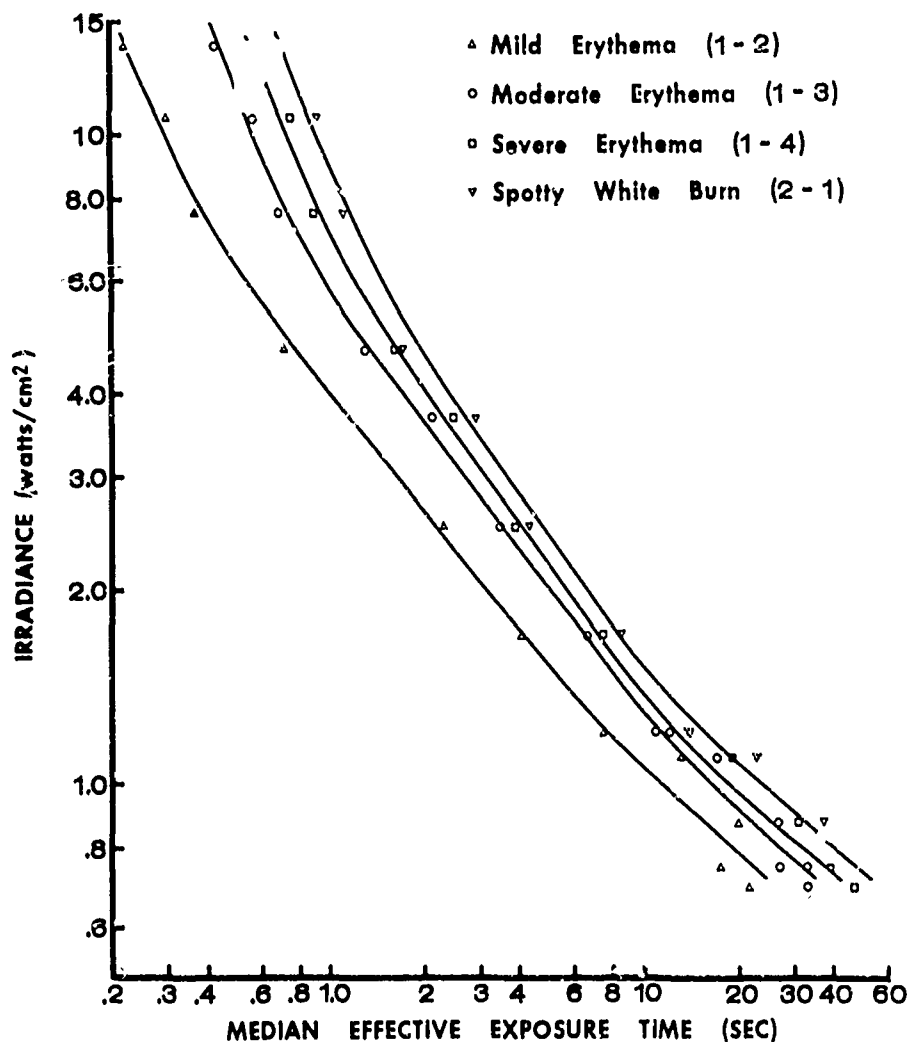


Fig. 2. Median effective exposure times vs. irradiance for thermal skin lesions.

values are tabulated in Table 3 (page 18) and graphically presented in the semilogarithmic plot of Figure 3 (next page). The data points are connected with solid lines to show the trend in each case.

The apparent plateau on the data curves in Figure 3 at short exposure times strongly suggests that the median effective radiant exposure necessary to produce these lesions will decrease little, if any, as the exposure time is further reduced. If this is the case, then for exposure times shorter than those shown, the ED<sub>50</sub> for mild erythema will be approximately 3 joules/cm² and 8 joules/cm² for partial white burns.

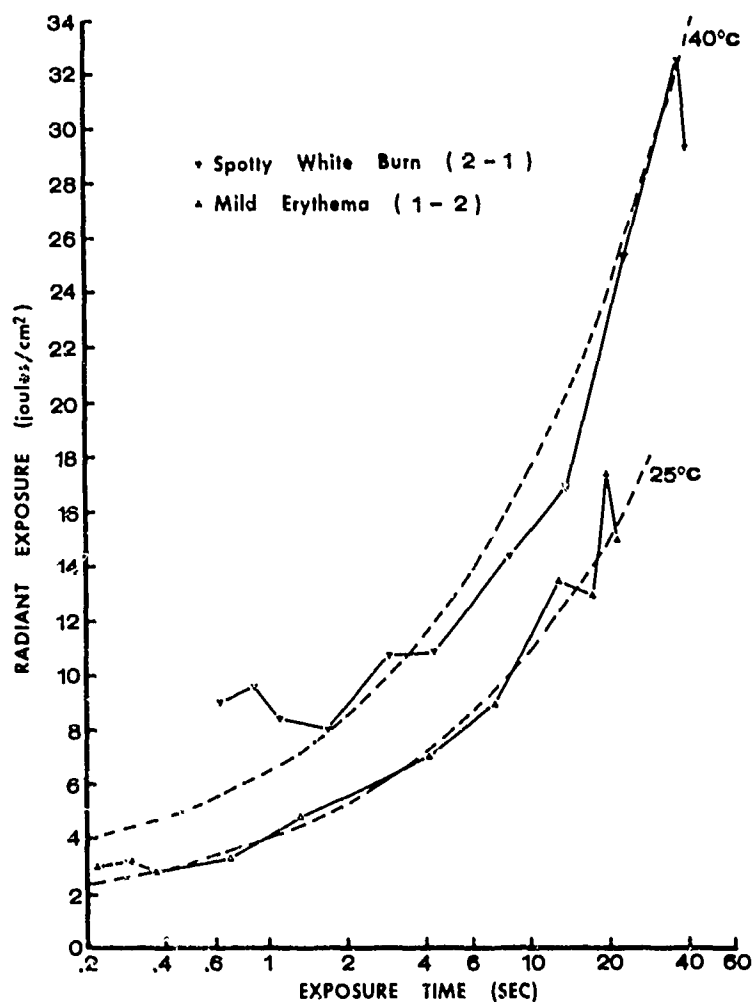


Fig. 3. Radiant exposure as a function of exposure time to produce thermal skin lesions. Dashed lines are theoretically derived; see text for explanation.

### DISCUSSION

The data for long exposure times and low irradiance shows considerable scatter (Fig. 2). Three possible explanations are suggested for the variability. It was previously mentioned that at low power levels the power output tended to fall off during the exposure period. Since the irradiance values given are the averages of the values determined before, during and following the experiments, there is increased uncertainty in the dosimetry at the lower irradiance levels. It can be seen in Figure 2 that in the lower irradiance range a small error in dosimetry could result in a big error in the median effective exposure time.

A second possibility for introducing variability in the data is variation in surface temperature of the porcine skin at the time of exposure. Berkley et al (3) found that if the skin temperature is lowered by 10°C the radiant exposure required to produce a comparable degree of damage increases by 30-40%. Barbiturates are known to affect the ability of animals to maintain their body temperature. The magnitude of this effect on the skin surface temperature in these experiments was not determined. Any variability in surface temperature could result in an alteration of the grade of burn for a given exposure.

Finally, the non-uniform distribution of energy flux in the laser beam could lead to errors in assessment of the appropriate irradiance. In some cases the irradiance pattern in the beam was duplicated in the erythema intensity in the skin. Apparently this was of more significance at low irradiance levels, when most of these cases were noted.

There is considerable interest in developing mathematical models to accurately predict the parameters resulting in specific radiation induced injuries over a wide range of wavelengths, exposure times and intensities (6-10). Recently, Peacock (9) formulated a mathematical model based on increases in surface temperature to predict threshold injuries induced by laser radiation. Although the model is successful in establishing worst case limits for safety standards, it falls short of accurately describing the radiation levels necessary to induce specific levels of thermal injury. The induction of thermal lesions in skin certainly is not uniquely a surface phenomenon and any model should include depth as a parameter.

An attempt is made with these data to make a simple correlation between tissue temperature and observed effect. It is assumed that the unique maximum temperature generated at the epidermal-dermal junction for a given exposure episode determines the specific extent of thermal injury to the tissue. The epidermal-dermal junction was chosen as representing the most appropriate depth because of the proximity of the dermal capillary bed, the role of the basal layer of the epithelium in regeneration of new tissue, and the morphologically distinct appearance of this junction.

In order to calculate the temperature rise at the epidermal-dermal junction, the following assumptions are made: the skin is a semi-infinite isotropic receiver, initially at a uniform temperature throughout; the thermal properties of the skin are constant and do not change with temperature; the surface is perfectly insulated and there are no reradiation losses; the radiation input is a square wave and is normal to and uniform

over the surface of the tissue. An additional assumption made is that the tissue is opaque to the radiation which is absorbed at the surface. The last assumption appears to be reasonable and should lead to a close approximation to the real system, since the half-layer value of wet tissue and water for 10.6 micron ( $\mu$ ) radiation is approximately  $10^{-3}$  cm with an absorption coefficient of about  $700 \text{ cm}^{-1}$  (11-12). Moreover, Peacock (9) has shown that the surface temperatures calculated by means of the opaque model agree with those calculated by means of the diathermous model. Agreement is to within 80% for exposures down to 0.1 sec when the thermal constants assumed here are used along with an absorption coefficient of  $700 \text{ cm}^{-1}$ .

Under these conditions the temperature rise during the exposure episode may be written (7, 8, 9) as

$$U(x, t) = \frac{8.36 I}{\sqrt{\mu}} \left[ \sqrt{\frac{t}{\pi}} e^{-x^2/4at} - \frac{x}{\sqrt{4a}} \operatorname{erfc}\left(\frac{x}{\sqrt{4at}}\right) \right]$$

Where  $U(x, t)$  = temperature rise at depth  $x$  and time  $t$

$I$  = irradiance ( $\text{joules sec}^{-1} \text{cm}^{-2}$ )

$t$  = exposure time (sec)

$x$  = tissue depth (cm)

$\mu$  = thermal inertia ( $\text{cal}^2 \text{cm}^{-2} \text{deg}^{-2} \text{sec}^{-1}$ )

$a$  = thermal diffusivity ( $\text{cm}^2 \text{sec}^{-1}$ )

$\operatorname{erfc}$  = complimentary error function

The values used for the thermal constants:

$$\mu = 11.7 \times 10^{-4} \text{cal}^2 \text{cm}^{-4} \text{deg}^{-2} \text{sec}^{-1}$$

$$a = 8.4 \times 10^{-4} \text{cm}^2 \text{sec}^{-1}$$

were those derived experimentally for pig skin by Davis (7, 8). The average depth of the epidermal-dermal junction was measured microscopically as  $75 \mu$  in biopsy samples taken from the skin of our experimental animals.

In Figure 3 the theoretical curve for a  $25^\circ \text{C}$  temperature rise shows a reasonably good fit to the experimental data for the production of mild erythema over the entire range tested. A  $40^\circ \text{C}$  temperature rise provides the curve which best fits the data for the white burn;

however, the fit is rather poor. It is obvious that this model is inadequate to accurately describe the dose-effect relationship for severe burns even over this limited exposure range.

Though the theoretical curve appears to have a good fit to the experimental data for mild erythema, its applicability over a wide range of exposure times is questionable. It was assumed that the maximum temperature at the epidermal-dermal junction uniquely determines the extent of the thermal injury. But Stoll and Greene (13) have shown for irradiance levels lower than those used in these experiments that the calculated maximum temperature at the epidermal-dermal junction of human skin to produce either threshold pain or threshold blisters increases with increasing irradiance. The assumption also ignores the time-temperature history of the epidermal-dermal junction and the contributions of the rest of the tissue in eliciting the measured response. Weaver and Stoll (10) concluded, from calculations made on the basis of the "damage integral" model (6), that the higher the irradiance the greater the contribution to thermal injury from the cooling portion of the temperature episode. Certainly the temperature gradient within the skin during the exposure period varies markedly with irradiance. Although in all cases for mild erythema the calculated maximum temperature rise at the epidermal-dermal junction is  $25^{\circ}\text{C}$ , the calculated maximum temperature rise at the surface of the tissue for equivalent exposure episodes is  $43.9^{\circ}\text{C}$  for  $12.4 \text{ watts/cm}^2$  (.2 sec exposure time) and  $26.3^{\circ}\text{C}$  for  $.75 \text{ watts/cm}^2$  (20 sec exposure time). Additional data, especially for very short exposure times, is needed to determine whether the proposed model will be useful in defining the exposure parameters necessary to produce threshold burns over a wide range of exposure conditions or that the goodness of fit shown here for a limited range is fortuitous.

The "damage integral" model takes into account the time-temperature history of the biological specimen and can easily be modified to accept thermal constants and damage rates which vary as a function of temperature. To evaluate the utility of the model for accurate predictions a computer program is being developed. This program will be used to analyze burn data from laser radiation over a wide range of exposure conditions and severity levels.

### CONCLUSIONS

The empirically determined dose-response relationship for the induction of thermal lesions in porcine skin by  $\text{CO}_2$  laser radiation is

adequate to establish laser safety standards for these injuries within the exposure time range of 0.2 to 40 sec.

A relatively simple model can describe, with reasonable accuracy, the exposure parameters necessary to produce threshold skin lesions within this same range of exposure times. However, the model is inadequate for more severe levels of injury.

Dose-response relationships should be determined at very short exposure times to determine the validity of extending the range of prediction of the model.

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TABLE 1

## Tabulated Dose-Response Data

Irradiance (watts/cm <sup>2</sup> )	Exposure Time (sec)	No. of Burns					Total
		0 or 1-1	1-2	1-3	1-4	2-1	
13.6	.06	15					15
	.11	17					17
	.16	14					14
	.21	8	7				15
	.25	3	12				15
	.30		17				17
	.35		13	2			15
	.40		9	6			15
	.50		3	7	4	1	15
	.60			2	10	4	16
	.70			1	1	13	15
	.79			1	1	13	15
	.89				2	14	16
10.6	.11	16					16
	.16	17					17
	.21	17					17
	.25	13	4				17
	.31	10	7				17
	.36	2	15				17
	.41	1	17				18
	.45	1	15				16
	.51		14	3			17
	.61		6	9	2		17
	.70		1	10	5	1	17
	.79			7	10	2	19
	.89			1	9	7	17
	.99			3	1	14	18
7.6	.39	5	6				11
	.49	4	18				22
	.59		18	4			22
	.68		12	10			22
	.79		2	16	4		22
	.88			4	6		10
	.99		2	2	16	2	22
	1.08				6	4	10



TABLE 1 (cont)

Irradiance (watts/cm <sup>2</sup> )	Exposure Time (sec)	No. of Burns					
		0 or 1-1	1-2	1-3	1-4	2-1	Total
	1.18			1	3	18	22
	1.29				2	7	9
	1.39					23	23
	1.48					10	10
	1.59					12	12
	1.78					12	12
	1.99					12	12
	.60	10	2				12
	.69	8	4				12
	.79	2	7				9
4.7	.90		11				11
	1.10		10	1			11
	1.30		5	10			15
	1.50		1	5	5		11
	1.70			3	3	6	12
	1.90				1	8	9
	2.10				2	10	12
	.38	12					12
	.49	12					12
	.60	12					12
3.7	.69	12					12
	.79	16	2				18
	.89	18					18
	.99	17	2				19
	1.20	11	1				12
	1.40	7	12				19
	1.60	2	15	1			18
	1.80	1	12	7			20
	2.00		11	7	1		19
	2.20	1	6	8	5		20
	2.41		3	6	7	3	19
	2.61		1	6	8	4	19
	2.81			6	5	8	19
	3.01			1	4	14	19
	3.21				1	17	18
	3.43					7	7

TABLE 1 (cont)

Irradiance (watts/cm <sup>2</sup> )	Exposure Time (sec)	No. of Burns					Total
		0 or 1-1	1-2	1-3	1-4	2-1	
2.5	1.40	12					12
	1.70	18					18
	2.00	16	2				18
	2.31	8	10				18
	2.61	1	17				18
	2.91	2	15	1			18
	3.22		14	1	1		16
	3.53		9	7		2	18
	3.83		4	5	6	3	18
	4.13		2	2	12	4	20
	4.43		1	2	3	11	17
	4.73			2	5	11	18
	4.94				2	17	19
	5.23			1	1	10	12
1.7	3.93	12	5				17
	4.23	6	15				21
	4.53	4	17				21
	4.84	5	16				21
	4.97	1	14				15
	5.24		18				18
	5.64		19				19
	6.02	1	11	1	1	1	15
	6.99		4	6	1	4	15
	8.02			4	6	5	15
	9.02			1	4	10	15
	10.0				2	13	15
	11.0					15	15
	12.0					15	15
1.2	4.96	14	1				15
	6.01	13	1				14
	6.98	10	5				15
	8.01	5	10				15
	9.01	1	14				15
	10.0		11	2	1		14
	11.0		6	6	1	1	14
	12.0		2	7	4	2	15

TABLE 1 (cont)

Irradiance (watts/cm <sup>2</sup> )	Exposure Time (sec)	No. of Burns					Total
		0 or 1-1	1-2	1-3	1-4	2-1	
1.1	8.03	15					15
	10.1	15					15
	12.0	12	3				15
	14.0	3	12				15
	16.0		11	4			15
	18.0		5	5	5		15
	20.0			8	6	1	15
	22.0			1	9	5	15
.87	10.3	10					10
	12.3	8					8
	14.4	10					10
	16.3	9	1				10
	18.3	7	3				10
	20.4	4	5				9
	23.3	1	7		1		9
	26.4		5	3	1		9
	29.3		2	3	3	1	9
	32.4		1	3	4	1	9
	35.5				5	4	9
	38.4				5	4	
	41.4				2	7	9
.74	15.4	16	2				18
	18.5	3	14	1			18
	21.6	1	14	1			16
	24.0	1	11	6			18
	27.7	1	7	9			17
	30.7		1	11	5		17
	33.7			8	7	3	18
	36.7			1	9	7	17
	38.9			1	5	11	17
	42.7				5	9	14
	45.8			3	3	12	18
	48.5				3	14	17
	51.6				3	14	17
	54.4				2	14	16

TABLE 1 (cont)

Irradiance (watts/cm <sup>2</sup> )	Exposure Time (sec)	No. of Burns					
		0 or 1-1	1-2	1-3	1-4	2-1	Total
.69	10.4	9					9
	12.3	10					10
	14.4	8					8
	16.5	8	1				9
	18.5	6	3				9
	20.4	8	3				11
	23.5	3	5	1			9
	26.1	1	7	2			10
	29.5	1	6	1			8
	32.3		6	2	1		9
	35.5		4	4	1		9
	38.3		2	5	2		9
	41.3			5	3		8

2,288

TABLE 2

Median Effective Exposure Times for Different Grades of Burn

Irradiance (watts/cm <sup>2</sup> )	EEt50 (Sec)			
	1-2	1-3	1-4	2-1
13.6	.22( .20- .24)*	.43( .39- .47)	.54( .49- .59)	.66( .61- .72)
10.6	.30( .28- .33)	.57( .54- .61)	.75( .70- .80)	.91( .87- .96)
7.6	.37( .32- .43)	.69( .65- .73)	.88( .84- .92)	1.1 ( 1.0 - 1.2 )
4.7	.71( .55- .77)	1.3 ( 1.2 - 1.4 )	1.6 ( 1.5 - 1.7 )	1.7 ( 1.6 - 1.9 )
3.7	1.3 ( 1.1 - 1.5 )	2.1 ( 2.0 - 2.2 )	2.5 ( 2.4 - 2.6 )	2.9 ( 2.8 - 3.0 )
2.5	2.3 ( 2.1 - 2.4 )	3.5 ( 3.4 - 3.7 )	3.9 ( 3.7 - 4.0 )	4.3 ( 4.1 - 4.5 )
1.7	4.1 ( 3.8 - 4.5 )	6.6 ( 6.3 - 6.9 )	7.5 ( 7.0 - 8.1)	8.4 ( 7.8 - 9.0 )
1.2	7.4 ( 6.9 - 8.0 )	10.8 (10.3 -11.4 )	12.2 (11.5 -12.9 )	14
1.1	13.1 (12.5 -13.8 )	17.2 (16.3 -18.1 )	19.4 (18.5 -20.4 )	23
.87	19.9 (78.6 -21.3 )	26.7 (24.4 -29.2 )	31.2 (28.5 -34.2 )	37.4 (34.7 -40.3 )
.74	17.4 (16.1 -18.9 )	27.0 (24.7 -29.5 )	33.0 (28.1 -38.0 )	39.6 (37.8 -41.5 )
.69	21.6 (19.8 -23.6 )	33.1 (30.2 -36.2 )	46.7 (43.5 -50.2 )	-

\* 95% confidence intervals are shown in parentheses.

TABLE 3

Radiant Energy to Produce 1-2 and 2-1 Burns

1-2 Burns		2-1 Burns	
Exposure Time (Sec)	Radiant Exposure (joules/cm <sup>2</sup> )	Exposure Time (Sec)	Radiant Exposure (joules/cm <sup>2</sup> )
.22	3.0	.66	9.0
.30	3.2	.91	9.6
.37	2.8	1.1	8.4
.71	3.3	1.7	8.0
1.3	4.8	2.9	10.7
2.3	5.8	4.3	10.8
4.1	7.0	8.4	14.3
7.4	8.9	14	17
13.1	14.4	23	25
17.4	12.9	37.4	32.5
19.9	17.3	39.6	29.3
21.6	14.9		

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13. ABSTRACT <p>Depilated skin of white pigs was exposed to different exposure time-irradiance combinations using CO<sub>2</sub> laser radiation (10.6 microns). The lesions produced ranged from a mild erythema to partial tissue coagulation. The probability of producing a particular grade of lesion was then established for power densities within the range of 0.69-13.6 watts/cm<sup>2</sup> and exposure times of 0.2 to 40 sec. Data obtained are adequate to establish laser safety standards. A relatively simple model is discussed that describes the exposure parameters to produce threshold skin lesions. (U)</p>		

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